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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/744,384	03/16/01	STUDER L	11613.0037US

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/744,384	Applicant(s) STUDER ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☒ Claim(s) *18,19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This action is in response to the Preliminary Amendment received January 23, 2001, Paper No. 7. Claims 1-19 are pending.

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e) as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Upon review of the specification of the parent provisional application and comparison with the specification of the present application, it is determined that the specification of parent provisional application 60/093,991 is not enabling for the use and preparation of the instantly claimed invention. The specification of the parent application does not teach or suggest the use of ascorbic acid in the differentiating medium, nor does it teach or suggest a cell culture comprising about 80 to 95% differentiated neuronal cells. The specification does not mention ascorbic acid at all. Since neither ascorbic acid nor a cell culture comprising 80 to 95% differentiated

neuronal cells are disclosed in the parent application and cannot be predicted from the teachings of the parent application, the parent application is not enabling for the instantly claimed invention. Thus, the requirements of the first paragraph of 35 U.S.C. §112 have not been met. Accordingly, claims 1-19 are assigned an effective filing date of July 23, 1999.

Drawings

2. The drawings are objected to because in Figure 1, "dissection" is misspelled. In Figure 3, "single" is misspelled. In Figure 5, "glutathione" is misspelled. Also in Figure 5, the two sets of data utilize the same filled in box therefore one cannot tell which data represents the ascorbic acid and which represents the glutathione. In Figure 6, "control" is misspelled twice. In Figure 8, there is an apparent typographical error in which "KCl/HBSS" is indicated as "KCl?HBSS".

Correction is required.

Specification

3. The disclosure is objected to because of the following informalities: A definition for the abbreviation "AA", used in Figure 6, is lacking on p. 2, lines 24-25. "Hydroxylase" is misspelled on p. 8, line 9, p. 10, line 14 and p. 19, line 7. A closing parentheses is apparently missing on p. 16, line 25. "Immunohistochemistry" is misspelled on p. 22, line 24. On p. 22, lines 28-30, there is what appears to be a table, however, it lacks column headings and there is no explanation for what "OSA-111",

"12501" or "24312" mean. On p. 23, the abbreviation "DA" is not defined. On p. 25, line 7, there is an incomplete sentence ending in "[?]".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. Claims 12,13 and 16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 12 encompasses a method of using cells cultured by proliferating CNS precursor cells in a medium with basic fibroblast growth factor (bFGF) and differentiating them in a medium containing ascorbic acid to yield aggregates of dopaminergic neuron cells to treat a patient with a neurological disorder. Claim 14 encompasses a method of introducing a gene product into a brain of a patient comprising transforming neuronal precursor cells, culturing as described and administering the transformed and cultured neuronal cells to a patient.

The nature of the invention is a method of treatment comprising the use of cultured neuronal cells cultured in a specific way. The cells used may also be transformed prior to culturing and treatment. The delivery of a nucleic acid in vivo or ex vivo for therapeutic reasons constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the

gene. While both references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; and Palù et al, pp. 10-11. Transplantation of untransformed neural tissue is also a very promising field of research but likewise, there are no documented successes.

The relative skill of those in the art of stem cell culture and recombinant DNA technology is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Neural tissue transplantation is also unpredictable, particularly in obtaining the correct type of cells needed to overcome a particular neurological disorder, as well maintaining survival and function of the grafted tissue.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. The specification discloses three specific neurological disorders for treatment using the cultured cells (Parkinson's disease, Alzheimer's and Huntington's disease) and a number of neurologically relevant polypeptides for use in gene therapy applications using the cultured cells. There is no

direction on how to sustain any therapeutic effect derived from simply grafting nontransformed neuronal cells into a brain. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. transient gene expression.

The working examples disclosed directed toward in vivo treatment is the use of rat embryonic CNS precursor cells, cultured according to the invention, and injected into rats having a chemical lesion in a specific part of their brain. The treated rats where then examined over the course of several months for a specific behavioral changes in amphetamine-induced rotation behavior. The rat brains were also subsequently examined for survival of the injected cells. There is no working example of treatment of Parkinson's disease, or any other neurological disorder, in a human. There is no working example wherein in transformed cultured neuronal cells are injected into an animal.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method of gene therapy to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in neuronal cells, whether the effect could be exploited for treatment of a disease and how to get sufficient expression to induce at least some therapeutic effect. In order to determine how to use the method of treating a neurological disorder by grafting cultured, untransformed neuronal cells, one of skill in the art would have to determine how to obtain the particular needed cells to

overcome a given disorder, how to maintain any therapeutic response derived from the transplantation and how to sustain the survival of the grafted cells indefinitely. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed methods of treatment using cultured neuronal cells.

7. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for precursor cells obtained from the ventral mesencephalon of E12 rat embryos, does not reasonably provide enablement for any precursor cells obtained from any source including human fetal tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The present claims are very broad. Claim 1 encompasses a method of generating a cell culture comprising dopaminergic neuron cells by proliferating and differentiating any precursor cells. It is well known in the art that the physical structures of human brains and rodent brains during fetal development is markedly different. The specification provides no evidence that the culture method would work on any precursor

cell, rather than just on CNS precursor cells. Furthermore the specification provides no evidence that precursor cells obtained from human embryonic tissue between embryonic week 5 to embryonic week 8 would develop dopaminergic neuron cells in the culturing method taught. The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed culturing method.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed methods of generating cultured neuronal cells using any precursor cell from any source other than precursor cells obtained from the ventral mesencephalon of E12 rat embryos.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite as it lacks a step which clearly relates back to the preamble.

Claim 12 provides for the use of cells cultured according to claim 1 to treat a patient with a neurological disorder, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 is vague and indefinite as it lacks a step which clearly relates back to the preamble.

Claim 16 provides for the use of cells cultured according to claim 1 in an assay, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claim 17 is rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (USP 5,792,900). Lee et al teach a cell culture of NT2N neurons which is over 99%

pure. The culture therefore comprises less than 5% glial cells. See col. 9, lines 36-39 and Table 2.

12. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Johe et al (Genes & Development (1996) 10:3129-3140). Johe et al teach a cell culture of bFGF-expanded embryonic clones comprising 81% of MAP2-immunoreactive cells (indicative of differentiated neuronal cells) and 2.0% GFAP-immunoreactive cells (marker for astroglial cells). See p. 3134, Table 3, +PDGF column for section A.

13. Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Deloulme et al (J. Neuroscience Research (1991) 29:499-509). Deloulme et al teach a cell culture of bFGF-expanded clones comprising 95% of NSE-immunoreactive cells (indicative of differentiated neuronal cells) and 4.0% GFAP-immunoreactive cells (marker for astroglial cells). See p. 503, second column, first paragraph.

Conclusion

Claims 1-17 are rejected. Claims 1-16, 18 and 19 are free of prior art. Claims 18 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's

representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

July 30, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER